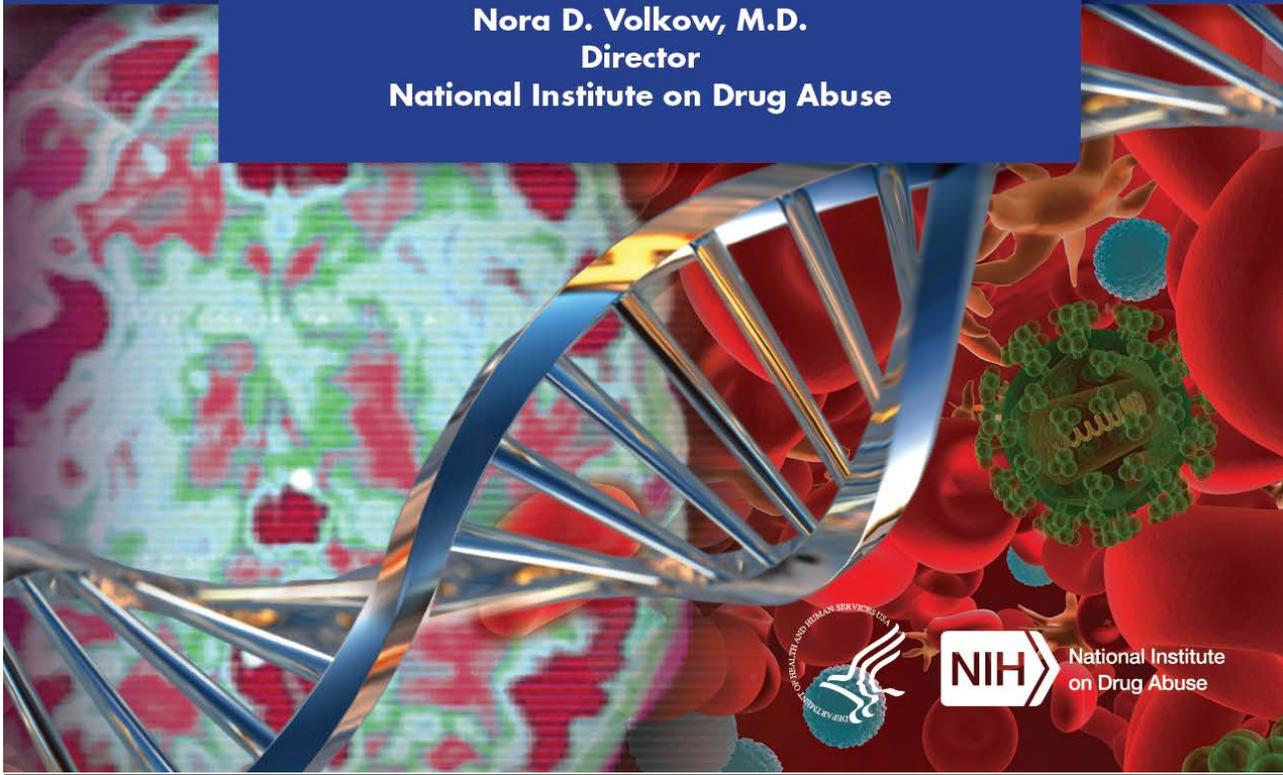




DIRECTOR'S REPORT

————— *to the* —————
National Advisory Council on Drug Abuse
————— *May 2018* —————

Nora D. Volkow, M.D.
Director
National Institute on Drug Abuse



National Institute
on Drug Abuse

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RESEARCH FINDINGS

BASIC AND BEHAVIORAL RESEARCH

Interrogating the Spatiotemporal Landscape Of Neuromodulatory GPCR Signaling By Real-Time Imaging Of cAMP In Intact Neurons and Circuits

Muntean, Brian S; Zucca, Stefano; MacMullen, Courtney M; Dao, Maria T; Johnston, Caitlin; Iwamoto, Hideki; Blakely, Randy D; Davis, Ronald L; Martemyanov, Kirill A. Cell Rep. 2018; 22(1): 255-268.

Modulation of neuronal circuits is key to information processing in the brain. The majority of neuromodulators exert their effects by activating G-protein-coupled receptors (GPCRs) that control the production of second messengers directly impacting cellular physiology. How numerous GPCRs integrate neuromodulatory inputs while accommodating diversity of incoming signals is poorly understood. In this study, the authors develop an in vivo tool and analytical suite for analyzing GPCR responses by monitoring the dynamics of a key second messenger, cyclic AMP (cAMP), with excellent quantitative and spatiotemporal resolution in various neurons. Using this imaging approach in combination with CRISPR/Cas9 editing and optogenetics, the authors interrogate neuromodulatory mechanisms of defined populations of neurons in an intact mesolimbic reward circuit and describe how individual inputs generate discrete second-messenger signatures in a cell- and receptor-specific fashion. This offers a resource for studying native neuronal GPCR signaling in real time.

K-Opioid Receptor Activation In Dopamine Neurons Disrupts Behavioral Inhibition

Abraham, Antony D; Fontaine, Harrison M; Song, Allisa J; Andrews, Mackenzie M; Baird, Madison A; Kieffer, Brigitte L; Land, Benjamin B; Chavkin, Charles. Neuropsychopharmacology. 2018; 43(2): 362-372.

The dynorphin/ κ -opioid receptor (KOR) system has been previously implicated in the regulation of cognition, but the neural circuitry and molecular mechanisms underlying KOR-mediated cognitive disruption are unknown. Here, the authors used an operational test of cognition involving timing and behavioral inhibition and found that systemic KOR activation impairs performance of male and female C57BL/6 mice in the differential reinforcement of low response rate (DRL) task. Systemic KOR antagonism also blocked stress-induced disruptions of DRL performance. KOR activation increased bursts of incorrect responses in the DRL task and increased marble burying, suggesting that the observed disruptions in DRL performance may be attributed to KOR-induced increases in compulsive behavior. Local inactivation of KOR by injection of the long-acting antagonist nor-BNI in the ventral tegmental area (VTA), but not the infralimbic prefrontal cortex (PFC) or dorsal raphe nucleus (DRN), prevented disruption of DRL performance caused by systemic KOR activation. Cre-dependent genetic excision of KOR from dopaminergic, but not serotonergic neurons, also blocked KOR-mediated disruption of DRL performance. At the molecular level, the authors found that these disruptive effects did not require arrestin-dependent signaling, because neither global deletion of G-protein receptor kinase 3 (GRK3) nor cell-specific deletion of GRK3/arrestin-dependent p38 α MAPK from dopamine neurons blocked KOR-mediated DRL disruptions. They then showed that nalfurafine, a clinically available G-biased KOR agonist, could also produce DRL disruptions. Together, these studies demonstrate that KOR activation in VTA dopamine neurons disrupts behavioral inhibition in a GRK3/arrestin-independent manner and suggests that KOR antagonists could be beneficial for decreasing stress-induced compulsive behaviors.

Amphetamine Reverses Escalated Cocaine Intake Via Restoration Of Dopamine Transporter Conformation Siciliano, Cody A; Saha, Kaustuv; Calipari, Erin S; Fordahl, Steve C; Chen, Rong; Khoshbouei, Habibeh; Jones, Sara R. *J Neurosci.* 2018; 38(2): 484-497.

Cocaine abuse disrupts dopamine system function, and reduces cocaine inhibition of the dopamine transporter (DAT), which results in tolerance. Although tolerance is a hallmark of cocaine addiction and a DSM-V criterion for substance abuse disorders, the molecular adaptations producing tolerance are unknown, and testing the impact of DAT changes on drug taking behaviors has proven difficult. In regard to treatment, amphetamine has shown efficacy in reducing cocaine intake; however, the mechanisms underlying these effects have not been explored. The goals of this study were twofold; the authors sought to (1) identify the molecular mechanisms by which cocaine exposure produces tolerance and (2) determine whether amphetamine-induced reductions in cocaine intake are connected to these mechanisms. Using cocaine self-administration and fast-scan cyclic voltammetry in male rats, the authors show that low-dose, continuous amphetamine treatment, during self-administration or abstinence, completely reversed cocaine tolerance. Amphetamine treatment also reversed escalated cocaine intake and decreased motivation to obtain cocaine as measured in a behavioral economics task, thereby linking tolerance to multiple facets of cocaine use. Finally, using fluorescence resonance energy transfer imaging, the authors found that cocaine tolerance is associated with the formation of DAT-DAT complexes, and that amphetamine disperses these complexes. In addition to extending our basic understanding of DATs and their role in cocaine reinforcement, they serendipitously identified a novel therapeutic target: DAT oligomer complexes. The authors show that dispersion of oligomers is concomitant with reduced cocaine intake, and propose that pharmacotherapeutics aimed at these complexes may have potential for cocaine addiction treatment. Tolerance to cocaine's subjective effects is a cardinal symptom of cocaine addiction and a DSM-V criterion for substance abuse disorders. However, elucidating the molecular adaptations that produce tolerance and determining its behavioral impact have proven difficult. Using cocaine self-administration in rats, the authors link tolerance to cocaine effects at the dopamine transporter (DAT) with aberrant cocaine-taking behaviors. Further, tolerance was associated with multi-DAT complexes, which formed after cocaine exposure. Treatment with amphetamine deconstructed DAT complexes, reversed tolerance, and decreased cocaine seeking. These data describe the behavioral consequence of cocaine tolerance, provide a putative mechanism for its development, and suggest that compounds that disperse DAT complexes may be efficacious treatments for cocaine addiction.

Retrograde Inhibition By A Specific Subset Of Interpeduncular $\alpha 5$ Nicotinic Neurons Regulates Nicotine Preference Ables, Jessica L; Görlich, Andreas; Antolin-Fontes, Beatriz; Wang, Cuidong; Lipford, Sylvia M; Riad, Michael H; Ren, Jing; Hu, Fei; Luo, Minmin; Kenny, Paul J; Heintz, Nathaniel; Ibañez-Tallon, Ines. *Proc Natl Acad Sci U S A.* 2017; 114(49): 13012-13017.

Repeated exposure to drugs of abuse can produce adaptive changes that lead to the establishment of dependence. It has been shown that allelic variation in the $\alpha 5$ nicotinic acetylcholine receptor (nAChR) gene *CHRNA5* is associated with higher risk of tobacco dependence. In the brain, $\alpha 5$ -containing nAChRs are expressed at very high levels in the interpeduncular nucleus (IPN). Here the authors identified two nonoverlapping $\alpha 5$ + cell populations ($\alpha 5$ - Amigo1 and $\alpha 5$ - Epyc) in mouse IPN that respond differentially to nicotine. Chronic nicotine treatment altered the translational profile of more than 1,000 genes in $\alpha 5$ - Amigo1 neurons, including neuronal nitric oxide synthase (Nos1) and somatostatin (Sst). In contrast, expression of few genes was altered in the $\alpha 5$ - Epyc population. The authors show that both nitric oxide and SST suppress optically evoked neurotransmitter release from the terminals of habenular (Hb) neurons in IPN. Moreover, in vivo silencing of neurotransmitter release from the $\alpha 5$ - Amigo1 but not from the $\alpha 5$ - Epyc population

eliminates nicotine reward, measured using place preference. This loss of nicotine reward was mimicked by shRNA-mediated knockdown of *Nos1* in the IPN. These findings reveal a proaddiction adaptive response to chronic nicotine in which nitric oxide and SST are released by a specific $\alpha 5$ -neuronal population to provide retrograde inhibition of the Hb-IPN circuit and thereby enhance the motivational properties of nicotine.

Nanoparticulate Peptide Delivery Exclusively To the Brain Produces Tolerance Free

Analgesia Lisa Godfrey, Antonio Iannitelli, Natalie L. Garrett, Julian Moger, Ian Imbert, Tamara King, Frank Porreca, Ramesh Soundararajan, Aikaterini Lalatsa, Andreas G. Schätzlein, Ijeoma F. Uchegbu. *Journal of Controlled Release*. 2018; 270:135-144.

The delivery of peptide drugs to the brain is challenging, principally due to the blood brain barrier and the low metabolic stability of peptides. Exclusive delivery to the brain with no peripheral exposure has hitherto not been demonstrated with brain quantification data. Here the authors show that polymer nanoparticles encapsulating leucine5-enkephalin hydrochloride (LENK) are able to transport LENK exclusively to the brain via the intranasal route, with no peripheral exposure and nanoparticle localisation is observed within the brain parenchyma. Animals dosed with LENK nanoparticles (NM0127) showed a strong anti-nociceptive response in multiple assays of evoked and on going pain whereas animals dosed intranasally with LENK alone were unresponsive. Animals did not develop tolerance to the anti-hyperalgesic activity of NM0127 and NM0127 was active in morphine tolerant animals. A microparticulate formulation of clustered nanoparticles was prepared to satisfy regulatory requirements for nasal dosage forms and the polymer nanoparticles alone were found to be biocompatible, via the nasal route, on chronic dosing.

EPIDEMIOLOGY, PREVENTION AND SERVICES RESEARCH

Association Of Noncigarette Tobacco Product Use With Future Cigarette Smoking Among Youth In The Population Assessment Of Tobacco And Health (PATH) Study, 2013-2015

Watkins, Shannon Lea; Glantz, Stanton A; Chaffee, Benjamin W. *JAMA Pediatr*. 2018; 172(2): 181-187.

Approximately 90% of adult smokers first tried a cigarette by 18 years of age, and even infrequent smoking in adolescence is associated with established adult smoking. Noncigarette tobacco use is increasing and could stimulate subsequent conventional cigarette smoking in youths. The objective of this study was to estimate the longitudinal association between noncigarette tobacco use and subsequent cigarette smoking initiation among US youth. In this prospective cohort study of the Population Assessment of Tobacco and Health (PATH) waves 1 (September 12, 2013, to December 14, 2014) and 2 (October 23, 2014, to October 30, 2015), a nationally representative sample of youths who never smoked a conventional cigarette at baseline and completed wave 2 follow-up (N = 10 384) was studied. PATH retention at follow-up was 87.9%. The measures collected were ever use and past 30-day use of electronic cigarettes (e-cigarettes), hookah, noncigarette combustible tobacco, or smokeless tobacco at baseline and ever use and past 30-day use of cigarettes at follow-up. The present analysis was based on the 10,384 PATH youth respondents who reported never having smoked a cigarette in wave 1 and whose cigarette ever or past 30-day use was reported in wave 2 (mean [SD] age, 14.3 [1.7] years; age range, 12-17 years; 5087 [49.1%] female; 4829 [52.5%] white). At 1-year follow-up, 469 (4.6%) of all baseline never-smoking youths had tried a cigarette and 219 (2.1%) had smoked a cigarette within the past 30 days. Cigarette ever use at follow-up was higher among youths who had ever used e-cigarettes (78 [19.1%]), hookah (60 [18.3%]), noncigarette combustible tobacco (45 [19.2%]), or smokeless tobacco (29 [18.8%]) at

baseline. After adjusting for sociodemographic, environmental, and behavioral smoking risk factors and for baseline ever use of other tobacco products, the odds of past 30-day cigarette use at follow-up were approximately twice as high among baseline ever users of e-cigarettes (odds ratio [OR], 1.87; 95% CI, 1.15-3.05), hookah (OR, 1.92; 95% CI, 1.17-3.17), noncigarette combustible tobacco (OR, 1.78; 95% CI, 1.00-3.19), and smokeless tobacco (OR, 2.07; 95% CI, 1.10-3.87). Youths who had tried more than 1 type of tobacco product at baseline had 3.81 (95% CI, 2.22-6.54) greater adjusted odds of past 30-day cigarette smoking at follow-up than did baseline never tobacco users. Any use of e-cigarettes, hookah, noncigarette combustible tobacco, or smokeless tobacco was independently associated with cigarette smoking 1 year later. Use of more than 1 product increased the odds of progressing to cigarette use.

[History of Medication-assisted Treatment and its Association with Initiating Others into Injection Drug Use in San Diego, CA](#) Mittal, Maria Luisa; Vashishtha, Devesh; Sun, Shelly; Jain, Sonia; Cuevas-Mota, Jazmine; Garfein, Richard; Strathdee, Steffanie A; Werb, Dan. *Subst Abuse Treat Prev Policy*. 2017; 12(1): 42.

Medication-assisted treatment (MAT) remains the gold standard for the treatment of opioid use disorder. MAT also reduces the frequency of injecting among people who inject drugs (PWID). Relatedly, data suggest that PWID play a key role in the initiation of others into drug injecting by exposing injecting practices to injection-naïve drug users. The authors' primary objective was to test whether a history of MAT enrollment is associated with a reduced odds of PWID providing injection initiation assistance. Preventing Injecting by Modifying Existing Responses (PRIMER; NIDA DP2-DA040256-01), is a multi-site cohort study assessing the impact of socio-structural factors on the risk that PWID provide injection initiation assistance. Data were drawn from a participating cohort of PWID in San Diego, CA. The primary outcome was reporting ever providing injection initiation assistance; the primary predictor was reporting ever being enrolled in MAT. Logistic regression was used to model associations between MAT enrollment and ever initiating others into injecting while adjusting for potential confounders. Participants (n = 354) were predominantly male (n = 249, 70%). Thirty-eight percent (n = 135) of participants reported ever initiating others into injection drug use. In multivariate analysis, participants who reported a history of MAT enrollment had significantly decreased odds of ever providing injection initiation assistance (Adjusted Odds Ratio [AOR]: 0.62, 95% Confidence Interval [CI]: 0.39-0.99). These preliminary findings suggest an association between MAT enrollment and a lower odds that male PWID report providing injection initiation assistance to injection-naïve drug users. Further research is needed to identify the pathways by which MAT enrollment may impact the risk that PWID initiate others into drug injecting.

[Intentional Cannabis Use to Reduce Crack Cocaine Use in a Canadian Setting: A Longitudinal Analysis](#) Socías, M Eugenia; Kerr, Thomas; Wood, Evan; Dong, Huiru; Lake, Stephanie; Hayashi, Kanna; DeBeck, Kora; Jutras-Aswad, Didier; Montaner, Julio; Milloy, M-J. *Addict Behav*. 2017; 72: 138-143.

No effective pharmacotherapies exist for the treatment of crack cocaine use disorders. Emerging data suggests that cannabinoids may play a role in reducing cocaine-related craving symptoms. This study investigated the intentional use of cannabis to reduce crack use among people who use illicit drugs (PWUD). Data were drawn from three prospective cohorts of PWUD in Vancouver, Canada. Using data from participants reporting intentional cannabis use to control crack use, the authors used generalized linear mixed-effects modeling to estimate the independent effect of three pre-defined intentional cannabis use periods (i.e., before, during and after first reported intentional use to reduce crack use) on frequency of crack use. Between 2012 and 2015, 122 participants reported

using cannabis to reduce crack use, contributing a total of 620 observations. In adjusted analyses, compared to before periods, after periods were associated with reduced frequency of crack use (Adjusted Odds Ratio [AOR]=1.89, 95% Confidence Interval [CI]: 1.02-3.45), but not the intentional use periods (AOR=0.85, 95% CI: 0.51-1.41). Frequency of cannabis use in after periods was higher than in before periods (AOR=4.72, 95% CI: 2.47-8.99), and showed a tendency to lower frequency than in intentional cannabis use periods (AOR=0.56, 95% CI: 0.32-1.01). A period of intentional cannabis use to reduce crack use was associated with decreased frequency of crack use in subsequent periods among PWUD. Further clinical research to assess the potential of cannabinoids for the treatment of crack use disorders is warranted.

Loose Regulation Of Medical Marijuana Programs Associated With Higher Rates Of Adult Marijuana Use But Not Cannabis Use Disorder Williams, Arthur Robin; Santaella-Tenorio, Julian; Mauro, Christine M; Levin, Frances R; Martins, Silvia S. *Addiction*. 2017; 112(11): 1985-1991.

Most US states have passed medical marijuana laws (MMLs), with great variation in program regulation impacting enrollment rates. The authors aimed to compare changes in rates of marijuana use, heavy use and cannabis use disorder across age groups while accounting for whether states enacted medicalized (highly regulated) or non-medical mml programs. Difference-in-differences estimates with time-varying state-level MML coded by program type (medicalized versus non-medical) were collected. Multi-level linear regression models adjusted for state-level random effects and covariates as well as historical trends in use. Nation-wide cross-sectional survey data from the US National Survey of Drug Use and Health (NSDUH) restricted use data portal aggregated at the state level. Participants comprised 2004-13 NSDUH respondents (n ~ 67 500/year); age groups 12-17, 18-25 and 26+ years. States had implemented eight medicalized and 15 non-medical MML programs. Primary outcome measures included (1) active (past-month) marijuana use; (2) heavy use (> 300 days/year); and (3) cannabis use disorder diagnosis, based on DSM-IV criteria. Covariates included program type, age group and state-level characteristics throughout the study period. Adults 26+ years of age living in states with non-medical MML programs increased past-month marijuana use 1.46% (from 4.13 to 6.59%, P = 0.01), skewing towards greater heavy marijuana by 2.36% (from 14.94 to 17.30, P = 0.09) after MMLs were enacted. However, no associated increase in the prevalence of cannabis use disorder was found during the study period. These findings do not show increases in prevalence of marijuana use among adults in states with medicalized MML programs. Additionally, there were no increases in adolescent or young adult marijuana outcomes following MML passage, irrespective of program type. Non-medical marijuana laws enacted in US states are associated with increased marijuana use, but only among adults aged 26+ years. Researchers and policymakers should consider program regulation and subgroup characteristics (i.e. demographics) when assessing for population level outcomes.

Prediction Of Future Chronic Opioid Use Among Hospitalized Patients Calcaterra, S L; Scarbro, S; Hull, M L; Forber, A D; Binswanger, I A; Colborn, K L. *J Gen Intern Med*. 2018. Opioids are commonly prescribed in the hospital; yet, little is known about which patients will progress to chronic opioid therapy (COT) following discharge. The authors defined COT as receipt of ≥ 90 -day supply of opioids with < 30-day gap in supply over a 180-day period or receipt of ≥ 10 opioid prescriptions over 1 year. Predictive tools to identify hospitalized patients at risk for future chronic opioid use could have clinical utility to improve pain management strategies and patient education during hospitalization and discharge. The objective of this study was to identify a parsimonious statistical model for predicting future COT among hospitalized patients not on COT before hospitalization. This was a retrospective analysis of electronic health record (EHR) data from

2008 to 2014 using logistic regression. Participants were hospitalized patients at an urban, safety net hospital. Independent variables included medical and mental health diagnoses, substance and tobacco use disorder, chronic or acute pain, surgical intervention during hospitalization, past year receipt of opioid or non-opioid analgesics or benzodiazepines, opioid receipt at hospital discharge, milligrams of morphine equivalents prescribed per hospital day, and others. Model prediction performance was estimated using area under the receiver operator curve, accuracy, sensitivity, and specificity. A model with 13 covariates was chosen using stepwise logistic regression on a randomly down-sampled subset of the data. Sensitivity and specificity were optimized using the Youden's index. This model predicted correctly COT in 79% of the patients and no COT correctly in 78% of the patients. This model accessed EHR data to predict 79% of the future COT among hospitalized patients. Application of such a predictive model within the EHR could identify patients at high risk for future chronic opioid use to allow clinicians to provide early patient education about pain management strategies and, when able, to wean opioids prior to discharge while incorporating alternative therapies for pain into discharge planning.

Polydrug Use and Its Association With Drug Treatment Outcomes Among Primary Heroin, Methamphetamine, and Cocaine Users Wang, Linwei; Min, Jeong Eun; Krebs, Emanuel; Evans, Elizabeth; Huang, David; Liu, Lei; Hser, Yih-Ing; Nosyk, Bohdan. *Int J Drug Policy*. 2017; 49: 32-40.

Polydrug use may challenge effective treatment for substance use disorders. The authors evaluate whether secondary substance use modifies the association between treatment and primary drug use among primary heroin, cocaine and methamphetamine (MA) users. Data were obtained from prospective cohort studies on people who use illicit drugs (PWUD) in California, USA. Using repeated monthly data on self-reported secondary substance use (heroin, cocaine, MA, alcohol or marijuana; ≥ 1 day in a month), primary drug use (≥ 1 day in a month), and treatment participation, collected via timeline follow-back, the authors fitted generalized linear mixed multiple regression models controlling for potential confounders to examine the interactions between treatment and secondary substance use on the odds of primary heroin, cocaine and MA use, respectively. Included in this study were 587 primary heroin, 444 primary MA, and 501 primary cocaine users, with a median of 32.4, 13.3 and 18.9 years of follow-up, respectively. In the absence of secondary substance use, treatment was strongly associated with decreased odds of primary drug use (adjusted odds ratios (aORs): 0.25, 95% CI: 0.24, 0.27, 0.07 (0.06, 0.08), and 0.07 (0.07, 0.09)) for primary heroin, MA, and cocaine users, respectively. Secondary substance use of any kind moderated these associations (0.82 (0.78, 0.87), 0.25 (0.21, 0.30) and 0.53 (0.45, 0.61), respectively), and these findings were consistent for each type of secondary substance considered. Moreover, the authors observed different associations in terms of direction and magnitude between secondary substance use and primary drug use during off-treatment periods across substance types. This study demonstrates secondary substance use moderates the temporal associations between treatment and primary drug use among primary heroin, MA and cocaine users. Disparate patterns of polydrug use require careful measurement and analysis to inform targeted treatment for polydrug users.

Psychosocial Functioning Among Regular Cannabis Users With and Without Cannabis Use Disorder Foster, Katherine T; Arterberry, Brooke J; Iacono, William G; McGue, Matt; Hicks, Brian M. *Psychol Med*. 2017; 1-9.

In the United States, cannabis accessibility has continued to rise as the perception of its harmfulness has decreased. Only about 30% of regular cannabis users develop cannabis use disorder (CUD), but it is unclear if individuals who use cannabis regularly without ever developing CUD experience notable psychosocial impairment across the lifespan. Therefore, psychosocial functioning was

compared across regular cannabis users with or without CUD and a non-user control group during adolescence (age 17; early risk) and young adulthood (ages 18-25; peak CUD prevalence). Weekly cannabis users with CUD (n = 311), weekly users without CUD (n = 111), and non-users (n = 996) were identified in the Minnesota Twin Family Study. Groups were compared on alcohol and illicit drug use, psychiatric problems, personality, and social functioning at age 17 and from ages 18 to 25. Self-reported cannabis use and problem use were independently verified using co-twin informant report. In both adolescence and young adulthood, non-CUD users reported significantly higher levels of substance use problems and externalizing behaviors than non-users, but lower levels than CUD users. High agreement between self- and co-twin informant reports confirmed the validity of self-reported cannabis use problems. Even in the absence of CUD, regular cannabis use was associated with psychosocial impairment in adolescence and young adulthood. However, regular users with CUD endorsed especially high psychiatric comorbidity and psychosocial impairment. The need for early prevention and intervention - regardless of CUD status - was highlighted by the presence of these patterns in adolescence.

[PROSPER Intervention Effects On Adolescents' Alcohol Misuse Vary By GABRA2 Genotype and Age](#) Russell, Michael A; Schlomer, Gabriel L; Cleveland, H Harrington; Feinberg, Mark E; Greenberg, Mark T; Spoth, Richard L; Redmond, Cleve; Vandenberg, David J. *Prev Sci.* 2018; 19(1): 27-37.

Preventive intervention effects on adolescent alcohol misuse may differ based on genotypes in gene-by-intervention (G x I) interactions, and these G x I interactions may vary as a function of age. The current study uses a novel statistical method, time-varying effect modeling (TVEM), to test an age-varying interaction between a single nucleotide polymorphism in the GABRA2 gene (rs279845) and a preventive intervention in predicting alcohol misuse in a longitudinal study of adolescents (ages 11-20). The preventive intervention was PROSPER, a community-based system for delivery of family and school programs selected from a menu of evidence-based interventions. TVEM results revealed a significant age-varying GABRA2 x intervention interaction from ages 12 to 18, with the peak effect size seen around age 13 (IRR = 0.50). The intervention significantly reduced alcohol misuse for adolescents with the GABRA2 TT genotype from ages 12.5 to 17 but did not reduce alcohol use for adolescents with the GABRA2 A allele at any age. Differences in intervention effects by GABRA2 genotype were most pronounced from ages 13 to 16-a period when drinking is associated with increased risk for alcohol use disorder. These findings provide additional evidence that intervention effects on adolescent alcohol misuse may differ by genotype, and provide novel evidence that the interaction between GABRA2 and intervention effects on alcohol use may vary with age. Implications for interventions targeting adolescent alcohol misuse are discussed.

[An Online Drug Abuse Prevention Program For Adolescent Girls: Posttest and 1-Year Outcomes](#) Schwinn, Traci M; Schinke, Steven P; Hopkins, Jessica; Keller, Bryan; Liu, Xiang. *J Youth Adolesc.* 2018; 47(3): 490-500.

Early adolescent girls' rates of drug use have matched, and in some instances, surpassed boys' rates. Though girls and boys share risk factors for drug use, girls also have gender-specific risks. Tailored interventions to prevent girls' drug use are warranted. This study developed and tested a web-based, drug abuse prevention program for adolescent girls. The nationwide sample of 13- and 14-year-old girls (N = 788) was recruited via Facebook ads. Enrolled girls were randomly assigned to the intervention or control condition. All girls completed pretest measures online. Following pretest, intervention girls interacted with the 9-session, gender-specific prevention program online. The program aimed to reduce girls' drug use and associated risk factors by improving their cognitive

and behavioral skills around such areas as coping with stress, managing mood, maintaining a healthy body image, and refusing drug use offers. Girls in both conditions again completed measures at posttest and 1-year follow-up. At posttest, and compared to girls in the control condition, girls who received the intervention smoked fewer cigarettes and reported higher self-esteem, goal setting, media literacy, and self-efficacy. At 1-year follow-up, and compared to girls in the control condition, girls who received the intervention reported engaging in less binge drinking and cigarette smoking; girls assigned to the intervention condition also had higher alcohol, cigarette, and marijuana refusal skills, coping skills, and media literacy and lower rates of peer drug use. This study's findings support the use of tailored, online drug abuse prevention programming for early adolescent girls.

Pathways Linking Adverse Childhood Experiences To Cigarette Smoking Among Young Black Men: A Prospective Analysis Of The Role Of Sleep Problems and Delayed Reward

Discounting Oshri, Assaf; Kogan, Steven; Liu, Sihong; Sweet, Lawrence; Mackillop, James. *Ann Behav Med.* 2017; 51(6): 890-898.

African American men experience increases in smoking during the young adult transition. Exposure to childhood adversity, a risk factor which disproportionately affects African American men, has been identified as a robust precursor to health risk behavior in general and cigarette smoking in particular. The intermediate mechanisms that transmit the influence of early adversity to smoking behavior are not well understood. The authors tested a model of the escalation of smoking behaviors among young adult African American men, investigating sleep disturbance and delayed reward discounting as intermediate factors linking adverse childhood experiences with smoking. Hypotheses were tested with three waves of data (Mage-T1 = 20.34, Mage-T2 = 21.92, Mage-T3 = 23.02) from 505 African American men living in rural counties in South Georgia. Men provided self-report data on their adverse childhood experiences, sleep problems, and smoking behavior using audio-assisted computer self-interviews. Men also completed a computer-based delayed reward discounting task. Structural equation modeling analyses supported our hypotheses: Adverse childhood experiences predicted poor sleep adequacy, which forecast increases in delayed reward discounting; discounting, in turn, predicted increased smoking. Significant indirect pathways were detected linking adversity to discounting via sleep adequacy and linking sleep adequacy to smoking via discounting. Prevention and intervention researchers can draw on these findings to develop programs that focus on sleep adequacy to reduce smoking in African American men exposed to childhood adversity.

Early Alcohol Use With Parental Permission: Psychosocial Characteristics and Drinking In Late Adolescence

Colder, Craig R; Shyhalla, Kathleen; Frndak, Seth E. *Addict Behav.* 2018; 76: 82-87.

The earliest experiences with alcohol for many children occur in the family context with parental supervision. The current study examined individual and sociocultural characteristics associated with early (prior to age 13years) sipping and tasting alcohol with parental permission in two longitudinal community samples. Early sipping/tasting was also tested as a predictor of frequency and quantity of alcohol use, and alcohol-related problems seven years later in late adolescence. Early sipping/tasting with parental permission was associated with a sociocultural context supportive of alcohol use (e.g., parental alcohol use, permissive rules about alcohol use in the home, parental attitudes about underage drinking, perceived peer norms), adolescent sensation seeking and disinhibition (e.g., surgency, externalizing behavior) and appraisals of alcohol (negative outcome expectancies and negative implicit alcohol associations). Early sipping/tasting predicted increased frequency and quantity of alcohol consumption, and increased alcohol-related problems in late

adolescence, even after controlling sociocultural and individual difference variables. Findings suggest that early sipping/tasting with parental permission is not benign and is a viable target for preventive interventions.

High HCV Cure Rates For People Who Use Drugs Treated With Direct Acting Antiviral Therapy At An Urban Primary Care Clinic

Brianna L. Norton, Julia Fleming, Marcus A. Bachhuber, Meredith Steinman, Joseph DeLuca, Chinazo O. Cunningham, Nirah Johnson, Fabienne Laraqe, Alain H. Litwin. *International Journal of Drug Policy* 47 (2017) 196–201. Though direct acting antivirals (DAAs) promise high cure rates, many providers and payers remain concerned about successful treatment for people who use drugs (PWUD), even among those engaged in opioid agonist treatment (OAT). The efficacy of DAAs among PWUD in real-world settings is unclear. The authors conducted a cohort study of patients initiating HCV treatment between January 2014 and August 2015 (n = 89) at a primary care clinic in the Bronx, NY. Onsite HCV treatment with DAAs was performed by an HCV specialist, with support from a care coordinator funded by the NYC Department of Health. The authors identified four categories of drug use and drug treatment: (1) no active drug use/not receiving OAT (defined as non-PWUD); (2) no active drug use/receiving OAT; (3) active drug use/not receiving OAT; and (4) active drug use/receiving OAT. The primary outcome was SVR at 12 weeks post-treatment. Results: Overall SVR rates were 95% (n = 41/43) for non-PWUD and 96% (n = 44/46) for patients actively using drugs and/or receiving OAT [p = 0.95]. There were no differences in SVR rates by drug use or drug treatment category. Compared to non-PWUD, those with no active drug use/receiving OAT had 100% SVR (n = 15/15; p = 1.0), those actively using drugs/not receiving OAT had 90% SVR (n = 9/10; p = 0.47), and those actively using drugs/receiving OAT had 95% SVR (20/21; p = 1.0). Regardless of active drug use or OAT, patients who received DAA therapy at an urban primary care clinic achieved high HCV cure rates. The authors found no clinical evidence to justify restricting access to HCV treatment for patients actively using drugs and/or receiving OAT.

Retention In Buprenorphine Treatment Is Associated With Improved HCV Care Outcomes

B.L. Norton, A. Beitin, M. Glenn, J. DeLuca, A.H. Litwin, C.O. Cunningham. *J Substance Abuse Treatment* 75 (2017): 38-42.

Persons who inject drugs, most of whom are opioid dependent, comprise the majority of the HCV infected in the United States. As the national opioid epidemic unfolds, increasing numbers of people are entering the medical system to access treatment for opioid use disorder, specifically with buprenorphine. Yet little is known about HCV care in patients accessing buprenorphine-based opioid treatment. The authors sought to determine the HCV prevalence, cascade of care, and the association between patient characteristics and completion of HCV cascade of care milestones for patients initiating buprenorphine treatment. The authors reviewed electronic health records of all patients who initiated buprenorphine treatment at a primary-care clinic in the Bronx, NY between January 2009 and January 2014. Of the 390 patients who initiated buprenorphine treatment, 123 were confirmed to have chronic HCV infection. The only patient characteristic associated with achieving HCV care milestones was retention in opioid treatment. Patients retained (vs. not retained) in buprenorphine treatment were more likely to be referred for HCV specialty care (63.1% vs. 34.0%, p b 0.01), achieve an HCV-specific evaluation (40.8% vs. 21.3%, p b 0.05), be offered HCV treatment (22.4% vs. 8.5%, p b 0.05), and initiate HCV treatment (9.2% vs. 6.4%, p = 0.6). Given the current opioid epidemic in the US and the growing number of people receiving buprenorphine treatment, there is an unprecedented opportunity to access and treat persons with HCV, reducing HCV transmission, morbidity and mortality. Retention in opioid treatment may

improve linkage and retention in HCV care; innovative models of care that integrate opioid drug treatment with HCV treatment are essential.

TREATMENT RESEARCH

Long-Lasting In Vivo Effects Of The Cannabinoid CB1 Antagonist AM6538 Paronis, Carol A; Chopda, Girish R; Vemuri, Kiran; Zakarian, Ani S; Makriyannis, Alexandros; Bergman, Jack. J Pharmacol Exp Ther. 2018; 364(3): 485-493.

AM6538 is a cannabinoid antagonist that binds CB1 receptors expressed in HEK-293 cells in a wash-resistant manner. The effects of AM6538 in live animals has not previously been established. The authors characterized the antagonist effects of AM6538 in male mice, using a warm-water tail-withdrawal assay, and in male squirrel monkeys trained to discriminate the CB1 agonist AM4054 from vehicle. The cannabinoid agonists WIN 55,212, Δ^9 -tetrahydrocannabinol (THC), and AM4054 all produced 100% maximum possible antinociceptive effects in mice following vehicle pretreatment. One-hour pretreatment with increasing doses of AM6538 (0.1-10 mg/kg) produced first rightward, then downward shifts of the agonist dose-effect functions. Rimonabant, 1-10 mg/kg, produced parallel rightward shifts of the AM4054 dose-effect functions, and baseline effects of AM4054 were nearly recovered within 24 hours following 10 mg/kg of rimonabant. In contrast, in mice treated with 10 mg/kg of AM6538, antagonism of THC or AM4054 lasted up to 7 days. AM6538 also antagonized the discriminative stimulus effects of AM4054 in squirrel monkeys in a dose-related manner, and the effects of 3.2 mg/kg of AM6538 endured for more than 7 days. The effective reduction in CB1 receptor reserve was used to calculate the relative efficacy (tau values) of WIN 55,212, THC, and AM4054 in mice and of AM4054 monkeys, with results indicating that THC has a lower efficacy than WIN 55,212 or AM4054 in mice. These results demonstrate that AM6538 is a long-acting CB antagonist in vivo, and further suggest that differences in CB efficacy can be revealed in behavioral assays following AM6538 treatment.

Varenicline and GZ-793A Differentially Decrease Methamphetamine Self-administration Under A Multiple Schedule Of Reinforcement In Rats Kangiser, Megan M; Dvoskin, Linda P; Zheng, Guangrong; Crooks, Peter A; Stairs, Dustin J. Behav Pharmacol. 2018; 29(1): 87-97.

Methamphetamine is a potent psychostimulant with high abuse rates. Currently, there is no Food and Drug Administration-approved pharmacotherapy for methamphetamine addiction. Ideally, a pharmacotherapy should selectively decrease methamphetamine self-administration without affecting responding for other reinforcers. One way to test this is with the use of a multiple schedule of reinforcement, in which drug and food are available in alternating components within a session. The present study evaluated GZ-793A, a vesicular monoamine transporter-2 inhibitor, and varenicline, a partial agonist at $\alpha 4\beta 2$ and full agonist at $\alpha 7$ nicotinic acetylcholine receptors, for their ability to decrease methamphetamine and food self-administration using a multiple schedule of reinforcement. Male Sprague-Dawley rats self-administered methamphetamine (0.03 mg/kg/intravenous infusion) and food pellets under a multiple schedule of reinforcement. GZ-793A or varenicline was administered before multiple schedule sessions. GZ-793A (5 and 20 mg/kg) significantly decreased methamphetamine intake compared with saline and did not alter food-maintained responding. In contrast, varenicline decreased methamphetamine intake less specifically across time. The results suggest that vesicular monoamine transporter-2 inhibition may be a viable pharmacological target for the treatment of methamphetamine-use disorders.

Effects Of Lorcaserin (Belviq®) On Nicotine- and Food-maintained Responding In Non-human Primates

Jacobs, David S; Barkin, Claire E; Kohut, Michelle R; Bergman, Jack; Kohut, Stephen J. *Drug Alcohol Depend.* 2017; 181: 94-101.

Accumulating evidence suggests that the FDA-approved serotonin 5-HT_{2C} receptor agonist, lorcaserin (Belviq®), may be a promising candidate for the management of substance use disorders, including nicotine addiction. The present study was conducted to determine the efficacy and selectivity of acute or continuous lorcaserin treatment for decreasing the reinforcing effects of nicotine in a primate species. Adult rhesus monkeys (n=4) with a history of nicotine self-administration (>2years) responded for injections of nicotine (0.32-100µg/kg IV) or food pellets under a fixed-ratio schedule of reinforcement during daily 100-min sessions. When responding was stable, lorcaserin was administered either as an acute pretreatment (0.1-1.0mg/kg, IM) or by continuous infusion (0.1mg/kg/hr, SC for 3-5days). Daily activity patterns were also monitored immediately following experimental sessions. Results indicate that acute lorcaserin pretreatment produced significant and dose-dependent decreases in nicotine-maintained responding across a >100-fold range of self-administered nicotine doses. Continuous lorcaserin treatment decreased intake of 10µg/kg/inj nicotine to about 50% of baseline values. Food-maintained responding was only moderately decreased in 3 of 4 subjects after acute administration and unaffected in all subjects during continuous treatment. Daily activity also was significantly decreased-to ≤50% of control values-following experimental sessions in which acute lorcaserin was administered. These data indicate that lorcaserin reduces IV self-administration of nicotine at a dose that decreases motoric activity but less consistently disrupts food-maintained responding. Further research into lorcaserin's potential utility for the management of nicotine dependence is warranted.

Cannabinoid CB1 Discrimination: Effects Of Endocannabinoids and Catabolic Enzyme Inhibitors

Leonard, Michael Z; Alapafuja, Shakiru O; Ji, Lipin; Shukla, Vidyanand G; Liu, Yingpeng; Nikas, Spyros P; Makriyannis, Alexandros; Bergman, Jack; Kangas, Brian D. *J Pharmacol Exp Ther.* 2017; 363(3): 314-323.

An improved understanding of the endocannabinoid system has provided new avenues of drug discovery and development toward the management of pain and other behavioral maladies. Exogenous cannabinoid type 1 (CB1) receptor agonists such as Δ⁹-tetrahydrocannabinol are increasingly used for their medicinal actions; however, their utility is constrained by concern regarding abuse-related subjective effects. This has led to growing interest in the clinical benefit of indirectly enhancing the activity of the highly labile endocannabinoids N-arachidon-ylethanolamine [AEA (or anandamide)] and/or 2-arachidonoylglycerol (2-AG) via catabolic enzyme inhibition. The present studies were conducted to determine whether such actions can lead to CB1 agonist-like subjective effects, as reflected in CB1-related discriminative stimulus effects in laboratory subjects. Squirrel monkeys (n= 8) that discriminated the CB1 full agonist AM4054 (0.01 mg/kg) from vehicle were used to study, first, the inhibitors of fatty acid amide hydrolase (FAAH) or monoacylglycerol lipase (MGL) alone or in combination [FAAH (URB597, AM4303); MGL (AM4301); FAAH/MGL (JZL195, AM4302)] and, second, the ability of the endocannabinoids AEA and 2-AG to produce CB1 agonist-like effects when administered alone or after enzyme inhibition. Results indicate that CB1-related discriminative stimulus effects were produced by combined, but not selective, inhibition of FAAH and MGL, and that these effects were nonsurmountably antagonized by low doses of rimonabant. Additionally, FAAH or MGL inhibition revealed CB1-like subjective effects produced by AEA but not by 2-AG. Taken together, the present data suggest that therapeutic effects of combined, but not selective, enhancement of AEA or 2-AG activity via enzyme inhibition may be accompanied by CB1 receptor-mediated subjective effects.

Abstinence and Reduced Frequency Of Use Are Associated With Improvements In Quality Of Life Among Treatment-seekers With Cannabis Use Disorder Brezing, Christina A; Choi, C Jean; Pavlicova, Martina; Brooks, Daniel; Mahony, Amy L; Mariani, John J; Levin, Frances R. *Am J Addict.* 2018; 27(2): 101-107.

Many patients with cannabis use disorder (CUD) do not achieve or do not have abstinence as a goal of treatment, rather they reduce their use. Assessing outcome measures as they relate to functioning and reductions in cannabis use is an important area of study. Quality of life (QoL) shows promise as one such measure. Past studies have demonstrated gender differences in QoL and CUD. The authors aim to assess (1) the relationship between cannabis use and QoL and (2) gender effects in an outpatient medication treatment study for CUD. Data from an 11-weeks, double-blind, placebo-controlled trial of lofexidine and dronabinol for CUD (n = 62) was analyzed. Pearson's correlations between baseline QoL as measured with the Quality of Life, Enjoyment, and Satisfaction Questionnaire-Short Form (QLES-Q-SF) and cannabis use assessed with modified timeline follow-back (TLFB) were examined. Multiple linear regression models of cannabis use on end of study QLES-Q-SF were analyzed, while adjusting for baseline QLES-Q-SF, study arm, and gender. Moderation effects with gender were also tested. No significant association between baseline cannabis use and QoL was found. End of study abstinence ($F_{1,47} = 8.34, p = .006$) and reduced proportion of using days ($F_{1,47} = 9.48, p = .004$) were each significantly associated with end of study QoL. Reduction in grams ($F_{1,27} = 0.25, p = .62$) was not associated with QoL at end of study. Gender was not a significant moderator. Abstinence and lower frequency of use are associated with higher QoL, regardless of gender. This is the first time QoL has been demonstrated to change over the course of CUD medication treatment. QoL is an important outcome in CUD treatment. NCT01020019. (*Am J Addict* 2018;27:101-107).

Frequency and Correlates Of Sleep Disturbance In Methadone and Buprenorphine-maintained Patients Dunn, Kelly E; Finan, Patrick H; Andrew Tompkins, D; Strain, Eric C. *Addict Behav.* 2018; 76: 8-14.

Opioid use disorder (OUD) is a significant public health problem, and opioid maintenance treatment (OMT) on methadone or buprenorphine is a common approach. This study characterized sleep impairment in patients maintained on methadone or buprenorphine, and evaluated its association with psychiatric and medical comorbidities. Participants (N=185) maintained on methadone (N=125) or buprenorphine (N=60) for OUD completed the Medical Outcomes Study Sleep Scale (MOS) to provide a point-prevalence assessment of sleep impairment. Measures of lifetime problems and current functioning were also examined and compared as both a function of OMT and level of sleep impairment. Participants reported high levels of sleep impairment on the MOS, including not getting the amount of sleep they needed (42.9%), not sleeping enough to feel rested (39.6%) and trouble falling asleep (23.3%) or falling back asleep after waking (25.8%). Few differences were observed between OMT groups, and psychiatric dysfunction emerged as the most robust predictor of sleep impairment ratings. Patients with sleep impairment, independent of OMT medications, also reported current opioid withdrawal, psychiatric impairment, negative affect, and pain. Results demonstrate substantial and clinically-significant impairments in sleep that are associated with a variety of current problems that could impact OMT outcomes and decrease quality of life. Outcomes support the development of methods to improve sleep in OMT patients, and to examine the degree to which sleep improvements may be associated with improvements in mood and other health-related measures.

HIV/AIDS RELATED RESEARCH

Predictors Of Linkage To HIV Care and Viral Suppression After Release From Jails and Prisons: A Retrospective Cohort Study

Kelsey B Loeliger, Frederick L Altice, Mayur M Desai, Maria M Ciarleglio, Colleen Gallagher, Jaimie P Meyer. *Lancet HIV* 2018; 5: e96–106.

Incarceration provides an opportunity for engagement in HIV care but is associated with poor HIV treatment outcomes after release. The authors aimed to assess post-release linkage to HIV care (LTC) and the effect of transitional case management services. To create a retrospective cohort of all adults with HIV released from jails and prisons in Connecticut, USA (2007–14), the authors linked administrative custody and pharmacy databases with mandatory HIV/AIDS surveillance monitoring and case management data. They examined time to LTC (defined as first viral load measurement after release) and viral suppression at LTC. They used generalised estimating equations to show predictors of LTC within 14 days and 30 days of release. Among 3302 incarceration periods for 1350 individuals between 2007 and 2014, 672 (21%) of 3181 periods had LTC within 14 days of release, 1042 (34%) of 3064 had LTC within 30 days of release, and 301 (29%) of 1042 had detectable viral loads at LTC. Factors positively associated with LTC within 14 days of release are intermediate (31–364 days) incarceration duration (adjusted odds ratio 1.52; 95% CI 1.19–1.95), and transitional case management (1.65; 1.36–1.99), receipt of antiretroviral therapy during incarceration (1.39; 1.11–1.74), and two or more medical comorbidities (1.86; 1.48–2.36). Reincarceration (0.70; 0.56–0.88) and conditional release (0.62; 0.50–0.78) were negatively associated with LTC within 14 days. Hispanic ethnicity, bonded release, and psychiatric comorbidity were also associated with LTC within 30 days but reincarceration was not. Interpretation LTC after release is suboptimal but improves when inmates' medical, psychiatric, and case management needs are identified and addressed before release. People who are rapidly cycling through jail facilities are particularly vulnerable to missed linkage opportunities. The use of integrated programmes to align justice and health-care goals has great potential to improve long-term HIV treatment outcomes.

Effectiveness of a Peer Navigation Intervention to Sustain Viral Suppression Among HIV-Positive Men and Transgender Women Released From Jail: The LINK LA Randomized Clinical Trial

William E. Cunningham; Robert E. Weiss; Terry Nakazono; Mark A. Malek; Steve J. Shoptaw; Susan L. Ettner; Nina T. Harawa. *JAMA Intern Med.* 2018;178(4):542-553.

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Diagnosis of human immunodeficiency virus (HIV) infection, linkage and retention in care, and adherence to antiretroviral therapy are steps in the care continuum enabling consistent viral suppression for people living with HIV, extending longevity and preventing further transmission. While incarcerated, people living with HIV receive antiretroviral therapy and achieve viral suppression more consistently than after they are released. No interventions have shown sustained viral suppression after jail release. The objective of this study was to test the effect on viral suppression in released inmates of the manualized LINK LA (Linking Inmates to Care in Los Angeles) peer navigation intervention compared with standard transitional case management controls. This was a randomized clinical trial conducted from December 2012 through October 2016 with people living with HIV being released from Los Angeles (LA) County Jail. All participants were (1) 18 years or older; (2) either men or transgender women diagnosed with HIV; (3) English speaking; (4) selected for the transitional case management program prior to enrollment; (5) residing in LA County; and (6) eligible for antiretroviral therapy. The study's main outcome measure was a change in HIV viral suppression (<75 copies/mL) over a 12-month period. During the 12-session, 24-week LINK LA Peer Navigation intervention, trained peer navigators counseled

participants on goal setting and problem solving around barriers to HIV care and adherence, starting while the participants were still in jail. After their release, they continued counseling while they accompanied participants to 2 HIV care visits, then facilitated communication with clinicians during visits. Of 356 participants randomized, 151 (42%) were black; 110 (31%) were Latino; 303 (85%) were men; 53 (15%) were transgender women; and the mean (SD) age was 39.5 (10.4) years. At 12 months, viral suppression was achieved by 62 (49.6%) of 125 participants in the peer navigation (intervention) arm compared with 45 (36.0%) of 125 in the transitional case management (control) arm, for an unadjusted treatment difference of 13.6% (95% CI, 1.34%-25.9%; $P = .03$). In the repeated measures, random effects, logistic model the adjusted probability of viral suppression declined from 52% at baseline to 30% among controls, while those in the peer navigation arm maintained viral suppression at 49% from baseline to 12 months, for a difference-in-difference of 22% (95% CI, 0.03-0.41; $P = .02$). The LINK LA peer navigation intervention was successful at preventing declines in viral suppression, typically seen after release from incarceration, compared with standard transitional case management. Future research should examine ways to strengthen the intervention to increase viral suppression above baseline levels. TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01406626.

[Aged Chinese-Origin Rhesus Macaques Infected With SIV Develop Marked Viremia In Absence Of Clinical Disease, Inflammation Or Cognitive Impairment](#) Bissel SJ, Gurnsey K, Jedema HP, Smith NF, Wang G, Bradberry CW, Wiley CA. *Retrovirology*. 2018 February 1; 15(1):17.

Damage to the central nervous system during HIV infection can lead to variable neurobehavioral dysfunction termed HIV-associated neurocognitive disorders (HAND). There is no clear consensus regarding the neuropathological or cellular basis of HAND. The authors sought to study the potential contribution of aging to the pathogenesis of HAND. Aged (range = 14.7-24.8 year) rhesus macaques of Chinese origin (RM-Ch) ($n = 23$) were trained to perform cognitive tasks. Macaques were then divided into four groups to assess the impact of SIV_{mac251} infection ($n = 12$) and combined antiretroviral therapy (CART) (5 infected; 5 mock-infected) on the execution of these tasks. Aged SIV-infected RM-Ch demonstrated significant plasma viremia and modest CSF viral loads but showed few clinical signs, no elevations of systemic temperature, and no changes in activity levels, platelet counts or weight. Concentrations of biomarkers of acute and chronic inflammation such as soluble CD14, CXCL10, IL-6 and TNF- α are known to be elevated following SIV infection of young adult macaques of several species, but concentrations of these biomarkers did not shift after SIV infection in aged RM-Ch and remained similar to mock-infected macaques. Neither acute nor chronic SIV infection or CART had a significant impact on accuracy, speed or percent completion in a sensorimotor test. Viremia in the absence of a chronic elevated inflammatory response seen in some aged RM-Ch is reminiscent of SIV infection in natural disease resistant hosts. The absence of cognitive impairment during SIV infection in aged RM-Ch might be in part attributed to diminishment of some facets of the immunological response. Additional study encompassing species and age differences is necessary to substantiate this hypothesis.

[Patterns of Substance Use and Arrest Histories Among Hospitalized HIV Drug Users: A Latent Class Analysis](#) Shiu-Yee K, Brincks AM, Feaster DJ, Frimpong JA, Nijhawan A, Mandler RN, Schwartz R, Del Rio C, Metsch LR. *AIDS Behav*. 2018 Jan 5. doi: 10.1007/s10461-017-2024-y. [Epub ahead of print].

Using baseline data from the NIDA Clinical Trials Network 0049 study (Project HOPE), the authors performed latent class analyses (LCA) to identify discrete classes, or clusters, of people living with HIV (PLWH) based on their past year substance use behaviors and lifetime arrest history. They also

performed multinomial logistic regressions to identify key characteristics associated with class membership. The authors identified 5 classes of substance users (minimal drug users, cocaine users, substantial cocaine/hazardous alcohol users, problem polysubstance users, substantial cocaine/heroin users) and 3 classes of arrest history (minimal arrests, non-drug arrests, drug-related arrests). While several demographic variables such as age and being Black or Hispanic were associated with class membership for some of the latent classes, participation in substance use treatment was the only covariate that was significantly associated with membership in all classes in both substance use and arrest history LCA models. The authors' analyses reveal complex patterns of behaviors among substance using PLWH and suggest that HIV intervention strategies may need to take into consideration such nuanced differences to better inform future studies and program implementation.

Network Analysis Of Hippocampal Neurons By Microelectrode Array In the Presence Of HIV-1 Tat and Cocaine

Ahooyi, Taha Mohseni; Shekarabi, Masoud; Decoppet, Emilie A; Langford, T Dianne; Khalili, Kamel. J Cell Physiol. Dec 5 2017; (PMID:29206302):

HIV-associated neurocognitive disorders affecting greater than 30% of patients are caused by HIV-1 infection of the CNS, and in part, include neurotoxic effects of the viral transactivator of transcription, Tat protein. In addition to increasing the risk for becoming HIV infected, cocaine abuse enhances the neuropathogenic impacts of HIV-1. To investigate the outcome of Tat and cocaine interference in the hippocampal neuronal network, microelectrode arrays were employed to develop a systematic framework to assess the rank-cross-correlation coefficient in cultured hippocampal neurons. Tat and cocaine differentially disturbed neuronal spiking rates, amplitude, synchronous activity and oscillations within the hippocampal neuronal network via potentiation of inhibitory neurotransmission. The Tat-mediated impairment of neuronal spiking was reversible by removal of Tat, which restored neuronal activity. The presence of astrocytes co-cultured with neuronal networks diminished the effects of Tat and cocaine on neuron function suggesting a role for astrocytes in stabilizing neuronal behavior and increasing neuronal spontaneous activities such as bursting amplitude, frequency and wave propagation rate. Taken together, these studies indicate that the HIV protein Tat and cocaine impair hippocampal neuronal network functioning and that the presence of astrocytes alleviates network dysfunction pointing to a newly discovered pathway through which ionic homeostasis is maintained by neuron-glia crosstalk in the CNS.

Creation Of A Nanoformulated Cabotegravir Prodrug With Improved Antiretroviral Profiles

Tian Zhou, Hang Su, Prasanta Dash, Zhiyi Lin, Bhagya Laxmi Dyavar Shetty, Ted Kocher, Adam Szlachetka, Benjamin Lamberty, Howard S. Fox, Larisa Poluektova, Santhi Gorantla, JoEllyn McMillan, Nagsen Gautam, R. Lee Mosley, Yazen Alnouti, Benson Edagwa, Howard E. Gendelman. Biomaterials 2018; 151:53-65.

Long-acting parenteral (LAP) antiretroviral drugs have generated considerable interest for treatment and prevention of HIV-1 infection. One new LAP is cabotegravir (CAB), a highly potent integrase inhibitor, with a half-life of up to 54 days, allowing for every other month parenteral administrations. Despite this excellent profile, high volume dosing, injection site reactions and low body fluid drug concentrations affect broad use for virus infected and susceptible people. To improve the drug delivery profile, the authors created a myristoylated CAB prodrug (MCAB). MCAB formed crystals that were formulated into nanoparticles (NMCAB) of stable size and shape facilitating avid monocyte-macrophage entry, retention and reticuloendothelial system depot formulation. Drug release kinetics paralleled sustained protection against HIV-1 challenge. After a single 45 mg/kg intramuscular injection to BALB/cJ mice, the NMCAB pharmacokinetic profiles was 4-times greater than that recorded for CAB LAP. These observations paralleled replicate

measurements in rhesus macaques. The results coupled with improved viral restriction in human adult lymphocyte reconstituted NOD/SCID/IL2R γ ^{-/-} mice led us to conclude that NMCAB can improve biodistribution and viral clearance profiles upon current CAB LAP formulations.

Cocaine Use May Induce Telomere Shortening In Individuals With HIV Infection

Lai, Shenghan; Heaphy, Christopher M; Rizzo, Anthony J; Celentano, David D; Gerstenblith, Gary; Li, Ji; Moore, Richard D; Treisman, Glenn; Chen, Shaoguang; Foster, Parker; Kickler, Thomas; Lai, Hong. *Prog Neuropsychopharmacol Biol Psychiatry*. 2018; 84(Pt A): 11-17.

Although cocaine use may induce/accelerate HIV-associated comorbidities in HIV-infected individuals on antiretroviral therapy (ART), and that HIV itself may accelerate aging, the issue of whether cocaine use plays a role in HIV-associated aging in HIV-infected cocaine users has not been reported. The goals of this study were (1) to explore factor(s) associated with peripheral blood leukocyte telomere length, a marker of cellular replicative history, and telomere shortening in HIV-infected individuals, and (2) to assess whether cocaine use plays a role in accelerating telomere shortening in cocaine users with HIV infection. Between June 2010 and December 2016, 147 HIV-infected participants in Baltimore, Maryland, were enrolled in a cross-sectional study investigating factor(s) associated with telomere length. Of these 147, 93 participated in a follow-up study to examine factor(s) associated with telomere shortening. Robust regression model was used to analyze cross-sectional data and the generalized estimating equation approach was used to analyze follow-up data. Cross-sectional analyses demonstrated that (1) both daily alcohol consumption and use of non-nucleoside reverse transcriptase inhibitors (NNRTIs) were independently associated with telomere length, and cocaine use modified the associations of daily alcohol use and NNRTI use with telomere length. Longitudinal analyses suggested that both daily alcohol consumption and duration of NNRTI use were independently associated with telomere shortening, and (2) cocaine use induced/accelerated telomere shortening in HIV-infected individuals. These findings suggest that cocaine use may promote premature aging in HIV-infected individuals who are on ART. The results emphasize the importance of cocaine abstinence/reduced use, which may retard HIV-associated premature aging.

Cannabis Use Is Associated With Lower Odds Of Prescription Opioid Analgesic Use Among HIV-Infected Individuals With Chronic Pain

Sohler, Nancy L; Starrels, Joanna L; Khalid, Laila; Bachhuber, Marcus A; Arnsten, Julia H; Nahvi, Shadi; Jost, John; Cunningham, Chinazo O. *Subst Use Misuse*. 2018; 1-6.

Chronic pain is common in the United States and prescribed opioid analgesics use for noncancer pain has increased dramatically in the past two decades, possibly accounting for the current opioid addiction epidemic. Co-morbid drug use in those prescribed opioid analgesics is common, but there are few data on polysubstance use patterns. The authors explored patterns of use of cigarette, alcohol, and illicit drugs in HIV-infected people with chronic pain who were prescribed opioid analgesics. They conducted a secondary data analysis of screening interviews conducted as part of a parent randomized trial of financial incentives to improve HIV outcomes among drug users. In a convenience sample of people with HIV and chronic pain, the authors collected self-report data on demographic characteristics; pain; patterns of opioid analgesic use (both prescribed and illicit); cigarette, alcohol, and illicit drug use (including cannabis, heroin, and cocaine) within the past 30 days; and current treatment for drug use and HIV. Almost half of the sample of people with HIV and chronic pain reported current prescribed opioid analgesic use (N = 372, 47.1%). Illicit drug use was common (N = 505, 63.9%), and cannabis was the most commonly used illicit substance (N = 311, 39.4%). In multivariate analyses, only cannabis use was significantly associated with lower odds of prescribed opioid analgesic use (adjusted odds ratio = 0.57; 95% confidence interval: 0.38-

0.87). These data suggest that new medical cannabis legislation might reduce the need for opioid analgesics for pain management, which could help to address adverse events associated with opioid analgesic use.

Sexual HIV Risk Behavior Outcomes Of Brief Interventions For Drug Use In An Inner-city Emergency Department: Secondary Outcomes From A Randomized Controlled Trial

Bonar, Erin E; Walton, Maureen A; Barry, Kristen L; Bohnert, Amy S B; Chermack, Stephen T; Cunningham, Rebecca M; Massey, Lynn S; Ignacio, Rosalinda V; Blow, Frederic C. *Drug Alcohol Depend.* 2018; 183: 217-224.

Drug use is an established risk factor for HIV. Brief Interventions (BIs) targeting reductions in both drug use and HIV risk behaviors may help curtail these related epidemics. The present study evaluates the impact of BIs for drug use and HIV risk reduction on sexual HIV risk behaviors among a primarily marijuana-using sample during a 12-month post-intervention follow-up period. The authors conducted a randomized controlled trial of 780 adult patients in an Emergency Department (ED) with past 3-month drug use (primarily non-injecting). This study used a 3×2 factorial design (3 ED-based conditions: computer-delivered brief intervention [Computer BI], therapist-delivered, computer-guided BI [Therapist BI], or enhanced usual care (EUC-ED) for drug-using adults; 2 follow-up conditions at 3 months: booster or control). This analysis examines the outcomes of the BIs on sexual HIV risk behaviors at 3-, 6-, and 12-months. Compared to the enhanced usual care control, the combined Therapist BI with booster resulted in significant reductions in scores on the sexual risk subscale of the HIV Risk Taking Behaviour Scale over 12-months, when controlling for baseline sexual risk, gender, and drug dependency status. The baseline interventions alone, booster alone, and Computer BI plus booster did not differ from the comparison group (EUC plus control). A therapist-delivered BI for drug use and HIV risk behaviors, combined with a follow-up therapist-delivered booster, shows promise for reducing sexual HIV risk behaviors among a primarily marijuana using, non-injecting sample.

CTN-RELATED RESEARCH

Substance Use Disorders and Medical Comorbidities Among High-Need, High-Risk Patients With Diabetes

Wu LT, Ghitza UE, Zhu H, Spratt S, Swartz M, Mannelli P. *Drug Alcohol Depend.* 2018 Mar 3;186:86-93. doi: 10.1016/j.drugalcdep.2018.01.008. [Epub ahead of print].

The majority of the U.S. healthcare resources are utilized by a small population characterized as high-risk, high-need persons with complex care needs (e.g., adults with multiple chronic conditions). Substance use disorders (SUDs) and mental health disorders (MHDs) are a driver of poor health and additional healthcare costs, but they are understudied among high-need patients. The authors examine the prevalence and correlates of SUDs and MHDs among adults with high-risk diabetes, who are patients at the top 10% risk score for developing poor outcomes (hospital admission or death). A risk algorithm developed from Duke University Health System electronic health records (EHRs) data was used to identify patients with high-risk diabetes for targeting home-based primary care. The EHR data of the 263 patients with high-risk diabetes were analyzed to understand patterns of SUDs and MHDs to inform care-coordinating efforts. Both SUDs (any SUD 48.3%, alcohol 12.5%, tobacco 38.8%, drug 23.2%) and MHDs (any MHD 74.9%, mood 53.2%, sleep 37.3%, anxiety 32.7%, schizophrenia/psychotics/delusional 14.8%, dementia/delirium/amnesic/cognitive 14.4%, adjustment 9.1%) were prevalent. Overall, 81.7% of the sample had SUD or MHD. Elevated odds of SUD were noted among men (tobacco, alcohol) and those who were never-married (alcohol, cannabis). African-American race (vs. other race/ethnicity) was

associated with lower odds of anxiety disorders. While data are limited to one large academic health system, they provide clinical evidence revealing that 82% of patients with high-risk diabetes had SUD and/or MHD recorded in their EHRs, highlighting a need for developing service models to optimize high-risk care.

Prevalence, Patterns, and Correlates Of Multiple Substance Use Disorders Among Adult Primary Care Patients

John WS, Zhu H, Mannelli P, Schwartz RP, Subramaniam GA, Wu LT. Drug Alcohol Depend. 2018 Mar 27;187:79-87. doi: 10.1016/j.drugalcdep.2018.01.035. [Epub ahead of print].

Addressing multiple substance use disorders (SUDs) in primary care-based screening and intervention may improve SUD treatment access, engagement, and outcomes. To inform such efforts, research is needed on the prevalence and patterns of multiple SUDs among primary care patients. Data were analyzed from a sample of 2000 adult (aged ≥ 18) primary care patients recruited for a multisite National Drug Abuse Treatment Clinical Trials Network (CTN) study (CTN-0059). Past-year DSM-5 SUDs (tobacco, alcohol, and drug) were assessed by the modified Composite International Diagnostic Interview. Prevalence and correlates of multiple versus single SUDs were examined. Latent class analysis (LCA) was used to explore patterns of multiple SUDs. Multiple SUDs were found among the majority of participants with SUD for alcohol, cannabis, prescription opioids, cocaine, and heroin. Participants who were male, ages 26-34, less educated, and unemployed had increased odds of multiple SUDs compared to one SUD. Having multiple SUDs was associated with greater severity of tobacco or alcohol use disorder. LCA of the sample identified three classes: class 1 (83.7%) exhibited low prevalence of all SUDs; class 2 (12.0%) had high-moderate prevalence of SUDs for tobacco, alcohol, and cannabis; class 3 (4.3%) showed high prevalence of SUD for tobacco, opioids, and cocaine. LCA-defined classes were distinguished by sex, age, race, education, and employment status. Findings suggest that primary care physicians should be aware of multiple SUDs when planning treatment, especially among adults who are male, younger, less educated, or unemployed. Interventions that target multiple SUDs warrant future investigation.

Incremental Validity Of Estimated Cannabis Grams As A Predictor Of Problems and Cannabinoid Biomarkers: Evidence From A Clinical Trial

Tomko RL, Baker NL, McClure EA, Sonne SC, McRae-Clark AL, Sherman BJ, Gray KM. Drug Alcohol Depend. 2018 Jan 1;182:1-7. doi: 10.1016/j.drugalcdep.2017.09.035. Epub 2017 Nov 2.

Quantifying cannabis use is complex due to a lack of a standardized packaging system that contains specified amounts of constituents. A laboratory procedure has been developed for estimating physical quantity of cannabis use by utilizing a surrogate substance to represent cannabis, and weighing the amount of the surrogate to determine typical use in grams.

This secondary analysis utilized data from a multi-site, randomized, controlled pharmacological trial for adult cannabis use disorder (N=300), sponsored by the National Drug Abuse Treatment Clinical Trials Network, to test the incremental validity of this procedure. In conjunction with the Timeline Followback, this physical scale-based procedure was used to determine whether average grams per cannabis administration predicted urine cannabinoid levels (11-nor-9-carboxy- Δ^9 -tetrahydrocannabinol) and problems due to use, after accounting for self-reported number of days used (in the past 30 days) and number of administrations per day in a 12-week clinical trial for cannabis use disorder. Likelihood ratio tests suggest that model fit was significantly improved when grams per administration and relevant interactions were included in the model predicting urine cannabinoid level ($X^2=98.3$; $p<0.05$) and in the model predicting problems due to cannabis use ($X^2=6.4$; $p<0.05$), relative to a model that contained only simpler measures of quantity and

frequency. This study provides support for the use of a scale-based method for quantifying cannabis use in grams. This methodology may be useful when precise quantification is necessary (e.g., measuring reduction in use in a clinical trial).

[Use Of A Prescription Opioid Registry To Examine Opioid Misuse and Overdose In An Integrated Health System](#) Campbell CI, Bahorik AL, VanVeldhuisen P, Weisner C, Rubinstein AL, Ray GT. *Prev Med.* 2018 May;110:31-37. doi: 10.1016/j.ypmed.2018.01.019. Epub 2018 Feb 2.

Strategies are needed to identify at-risk patients for adverse events associated with prescription opioids. This study identified prescription opioid misuse in an integrated health system using electronic health record (EHR) data, and examined predictors of misuse and overdose. The sample included patients from an EHR-based registry of adults who used prescription opioids in 2011 in Kaiser Permanente Northern California, a large integrated health care system. The authors characterized time-at-risk for opioid misuse and overdose, and used Cox proportional hazard models to model predictors of these events from 2011 to 2014. Among 396,452 patients, 2.7% were identified with opioid misuse and 1044 had an overdose event. Older patients were less likely to meet misuse criteria or have an overdose. Whites were more likely to be identified with misuse, but not to have an overdose. Alcohol and drug disorders were related to higher risk of misuse and overdose, with the exception that marijuana disorder was not related to opioid misuse. Higher daily opioid dosages and benzodiazepine use increased the risk of both opioid misuse and overdose. The authors characterized several risk factors associated with misuse and overdose using EHR-based data, which can be leveraged relatively quickly to inform preventive strategies to address the opioid crisis.

INTRAMURAL RESEARCH

[Gs- Versus Golf-Dependent Functional Selectivity Mediated By the Dopamine D₁ Receptor](#)

Yano H, Cai NS, Xu M, Verma RK, Rea W, Hoffman AF, Shi L, Javitch JA, Bonci A, Ferré S. *Nature Communication.* Feb 5;9(1):486, 2018.

The two highly homologous subtypes of stimulatory G proteins *G_s* (*G_s*) and *G_{αolf}* (*Golf*) display contrasting expression patterns in the brain. *Golf* is predominant in the striatum, while *G_s* is predominant in the cortex. Yet, little is known about their functional distinctions. The dopamine D₁ receptor (D₁R) couples to *G_{s/olf}* and is highly expressed in cortical and striatal areas, making it an important therapeutic target for neuropsychiatric disorders. Using novel drug screening methods that allow analysis of specific G-protein subtype coupling, the authors found that, relative to dopamine, dihydrexidine and N-propyl-apomorphine behave as full D₁R agonists when coupled to *G_s*, but as partial D₁R agonists when coupled to *Golf*. The *G_s/Golf*-dependent biased agonism by dihydrexidine was consistently observed at the levels of cellular signaling, neuronal function, and behavior. These findings of *G_s/Golf*-dependent functional selectivity in D₁R ligands open a new avenue for the treatment of cortex-specific or striatum-specific neuropsychiatric dysfunction.

[Graph Theory Reveals Amygdala Modules Consistent With Its Anatomical Subdivisions](#)

Caparelli EC, Ross TJ, Gu H, Liang X, Stein EA, Yang Y. *Sci Rep.* 2017 Oct 31; 7(1): 14392. Similarities on the cellular and neurochemical composition of the amygdaloid subnuclei suggests their clustering into subunits that exhibit unique functional organization. The topological principle of community structure has been used to identify functional subnetworks in neuroimaging data that reflect the brain effective organization. Here the authors used modularity to investigate the

organization of the amygdala using resting state functional magnetic resonance imaging (rsfMRI) data. Their goal was to determine whether such topological organization would reliably reflect the known neurobiology of individual amygdaloid nuclei, allowing for human imaging studies to accurately reflect the underlying neurobiology. Modularity analysis identified amygdaloid elements consistent with the main anatomical subdivisions of the amygdala that embody distinct functional and structural properties. Additionally, functional connectivity pathways of these subunits and their correlation with task-induced amygdala activation revealed distinct functional profiles consistent with the neurobiology of the amygdala nuclei. These modularity findings corroborate the structure–function relationship between amygdala anatomical substructures, supporting the use of network analysis techniques to generate biologically meaningful partitions of brain structures.

[Delta Rhythm Orchestrates the Neural Activity Underlying the Resting State BOLD Signal via Phase–amplitude Coupling](#)

Jaime S, Gu H, Sadacca BF, Stein EA, Cavazos JE, Yang Y, Lu H. *Cerebral Cortex*. 2017 Nov 17:1-15.

Spontaneous ongoing neuronal activity is a prominent feature of the mammalian brain. Temporal and spatial patterns of such ongoing activity have been exploited to examine large-scale brain network organization and function. However, the neurophysiological basis of this spontaneous brain activity as detected by resting-state functional Magnetic Resonance Imaging (fMRI) remains poorly understood. To this end, multi-site local field potentials (LFP) and blood oxygenation level dependent (BOLD) fMRI were simultaneously recorded in the rat striatum along with local pharmacological manipulation of striatal activity. Results demonstrate that delta (δ) band LFP power negatively, while beta (β) and gamma (γ) band LFPs positively correlated with BOLD fluctuation. Furthermore, there was strong cross-frequency phase–amplitude coupling (PAC), with the phase of δ LFPs significantly modulating the amplitude of the high frequency signal. Enhancing dopaminergic neuronal activity significantly reduced ventral striatal functional connectivity, δ LFP–BOLD correlation, and the PAC effect. These data suggest that different frequency bands of the LFP contribute distinctively to BOLD spontaneous fluctuation and that PAC is the organizing mechanism through which low frequency LFPs orchestrate neural activity that underlies resting state functional connectivity.

[A Novel Transcranial Magnetic Stimulator For Focal Stimulation Of Rodent Brain](#)

Meng Q, Jing L, Badjo JP, Du X, Hong E, Yang Y, Lu H, Choa FS. *Brain Stimulation*. 2018 Mar 1 [Epub ahead of print].

Transcranial magnetic stimulation (TMS) is emerging as a therapeutic tool for treating a number of neuropsychiatric disorders, however, its underlying mechanisms remain largely unknown. Due to potential safety and ethical concerns, studies to uncover the neurobiological mechanisms of TMS cannot be fully accomplished in humans, preclinical rodent studies are of great importance in this regard. The authors have developed an innovative concept to dramatically enhance the efficiency of TMS coil, a major challenge associated with small coil size; they have applied a new wire-wrapping method to break the circular symmetry of the field pattern, achieving focused electric field distribution. In vivo, experiments demonstrate reproducible contralateral single-limb activation and motor evoked potential (MEP).

[Orbitofrontal Neurons Signal Sensory Associations Underlying Model-Based Inference In A Sensory Preconditioning Task](#)

Sadacca BF, Wied, HM, Lopatina, N, Saini, GK, Nemirovsky, D, Schoenbaum, G. *ELIFE*. pii: e30373. doi: 10.7554/eLife.30373.

Using knowledge of the structure of the world to infer value is at the heart of model-based reasoning and relies on a circuit that includes the orbitofrontal cortex (OFC). Some accounts link

this to the representation of biological significance or value by neurons in OFC, while other models focus on the representation of associative structure or cognitive maps. Here the authors tested between these accounts by recording OFC neurons in rats during an OFC-dependent sensory preconditioning task. They found that while OFC neurons were strongly driven by biological significance or reward predictions at the end of training, they also showed clear evidence of acquiring the incidental stimulus-stimulus pairings in the preconditioning phase, prior to reward training. These results support a role for OFC in representing associative structure, independent of value.

[Lateral Preoptic Control of the Lateral Habenula through Convergent Glutamate and GABA Transmission](#) Barker DJ, Miranda-Barrientos J, Zhang S, Root DH, Wang HL, Liu B, Calipari ES, Morales M. Cell Reports Nov 14;21(7):1757-1769, 2017. doi: 10.1016/j.celrep.2017.10.066.

The lateral habenula (LHb) is a brain structure that participates in cognitive and emotional processing and has been implicated in several mental disorders. Although one of the largest inputs to the LHb originates in the lateral preoptic area (LPO), little is known about how the LPO participates in the regulation of LHb function. Here, the authors provide evidence that the LPO exerts bivalent control over the LHb through the convergent transmission of LPO glutamate and γ -aminobutyric acid (GABA) onto single LHb neurons. In vivo, both LPO-glutamatergic and LPO-GABAergic inputs to the LHb are activated by aversive stimuli, and their predictive cues yet produce opposing behaviors when stimulated independently. These results support a model wherein the balanced response of converging LPO-glutamate and LPO-GABA are necessary for a normal response to noxious stimuli, and an imbalance in LPO→LHb glutamate or GABA results in the type of aberrant processing that may underlie mental disorders.

[A Stable Heroin Analogue That Can Serve as a Vaccine Hapten to Induce Antibodies That Block the Effects of Heroin and Its Metabolites in Rodents and That Cross-React Immunologically with Related Drugs of Abuse](#) Sulima A, Jalah R, Antoline JFG, Torres OB, Imler GH, Deschamps JR, Beck Z, Alving CR, Jacobson AE, Rice KC, Matyas GR.. Journal of Medicinal Chemistry: Jan 11;61(1):329-343, 2018.

An improved synthesis of a haptenic heroin surrogate 1 (6-AmHap) is reported. The intermediate needed for the preparation of 1 was described in the route in the synthesis of 2 (DiAmHap). A scalable procedure was developed to install the C-3 amido group. Using the Boc protecting group in 18 allowed preparation of 1 in an overall yield of 53% from 4 and eliminated the necessity of preparing the diamide 13. Hapten 1 was conjugated to tetanus toxoid and mixed with liposomes containing monophosphoryl lipid A as an adjuvant. The 1 vaccine induced high anti-1 IgG levels that reduced heroin-induced antinociception and locomotive behavioral changes following repeated subcutaneous and intravenous heroin challenges in mice and rats. Vaccinated mice had reduced heroin-induced hyperlocomotion following a 50 mg/kg heroin challenge. The 1 vaccine-induced antibodies bound to heroin and other abused opioids, including hydrocodone, oxycodone, hydromorphone, oxymorphone, and codeine.

[Role Of Anterior Intralaminar Nuclei Of Thalamus Projections To Dorsomedial Striatum In Incubation Of Methamphetamine Craving](#) Li X, Witonsky K, Lofaro O, Surjono F, Zhang J, Bossert JM, Shaham Y The Journal of Neuroscience 2018; 38:2270-2282.

Relapse to methamphetamine (Meth) seeking progressively increases after withdrawal from drug self-administration (incubation of Meth craving). The authors previously demonstrated a role of dorsomedial striatum (DMS) dopamine D1 receptors (D1Rs) in this incubation. Here, they studied the role of afferent glutamatergic projections into DMS and local D1R-glutamate interaction in this

incubation in male rats. The authors first measured projection-specific activation on day 30 relapse test by using CTb (retrograde tracer) + Fos (activity marker) double-labeling in projection areas. Next, they determined the effect of pharmacological reversible inactivation of lateral or medial anterior intralaminar nuclei of thalamus (AIT-L or AIT-M) on incubated Meth seeking on withdrawal day 30. The authors then used an anatomical asymmetrical disconnection procedure to determine whether an interaction between AIT-L→DMS glutamatergic projections and post-synaptic DMS D1Rs contributes to incubated Meth seeking. They also determined the effect of unilateral inactivation of AIT-L and D1Rs blockade of DMS on incubated Meth seeking, and the effect of contralateral disconnection of AIT-L→DMS projections on non-incubated Meth seeking on withdrawal day 1. Incubated Meth seeking was associated with selective activation of AIT→DMS projections; other glutamatergic projections to DMS were not activated. AIT-L (but not AIT-M) inactivation or anatomical disconnection of AIT-L→DMS projections decreased incubated Meth seeking. Unilateral inactivation of AIT-L or D1Rs blockade of DMS had no effect on incubated Meth craving, and contralateral disconnection of AIT-L→DMS had no effect on non-incubated Meth seeking. These results identify a novel role of AIT-L and AIT-L→DMS glutamatergic projections in incubation of drug craving and drug seeking.

Post-stroke Intranasal (+)-Naloxone Delivery Reduces Microglial Activation and Improves Behavioral Recovery from Ischemic Injury

Jenni E. Anttila, Katrina Albert, Emily S. Wires, Kert Mätlik, Lisa Loram, Linda Watkins, Kenner C. Rice, Yun Wang, Brandon K. Harvey and Mikko Airavaara. *eNeuro* 16 April 2018, 5 (2) ENEURO.0395-17.2018.

Ischemic stroke is the leading cause of disability, and effective therapeutic strategies are needed to promote complete recovery. Neuroinflammation plays a significant role in stroke pathophysiology, and there is limited understanding of how it affects recovery. The aim of this study was to characterize the spatiotemporal expression profile of microglial activation and whether dampening microglial/macrophage activation post-stroke facilitates the recovery. For dampening microglial/macrophage activation, the authors chose intranasal administration of naloxone, a drug that is already in clinical use for opioid overdose and is known to decrease microglia/macrophage activation. They characterized the temporal progression of microglia/macrophage activation following cortical ischemic injury in rat and found the peak activation in cortex 7 d post-stroke. Unexpectedly, there was a chronic expression of phagocytic cells in the thalamus associated with neuronal loss. (+)-Naloxone, an enantiomer that reduces microglial activation without antagonizing opioid receptors, was administered intranasally starting 1 d post-stroke and continuing for 7 d. (+)-Naloxone treatment decreased microglia/macrophage activation in the striatum and thalamus, promoted behavioral recovery during the 14-d monitoring period, and reduced neuronal death in the lesioned cortex and ipsilateral thalamus. These results are the first to show that post-stroke intranasal (+)-naloxone administration promotes short-term functional recovery and reduces microglia/macrophage activation. Therefore, (+)-naloxone is a promising drug for the treatment of ischemic stroke, and further studies should be conducted.

Evidence For Functional Pre-Coupled Complexes Of Receptor Heteromers and Adenylyl Cyclase

Navarro G, Cordoní A, Casadó-Anguera V, Moreno E, Cai NS, Cortés A, Canela EI, Dessauer CW, Casadó V, Pardo L, Lluís C, Ferré S *Nat Commun* 2018 Mar 28;9(1):1242.

G protein-coupled receptors (GPCRs), G proteins and adenylyl cyclase (AC) comprise one of the most studied transmembrane cell signaling pathways. However, it is unknown whether the ligand-dependent interactions between these signaling molecules are based on random collisions or the rearrangement of pre-coupled elements in a macromolecular complex. Furthermore, it remains controversial whether a GPCR homodimer coupled to a single heterotrimeric G protein constitutes a

common functional unit. Using a peptide-based approach, the authors here report evidence for the existence of functional pre-coupled complexes of heteromers of adenosine A2A receptor and dopamine D2 receptor homodimers coupled to their cognate Gs and Gi proteins and to subtype 5 AC. They also demonstrate that this macromolecular complex provides the necessary frame for the canonical Gs-Gi interactions at the AC level, sustaining the ability of a Gi-coupled GPCR to counteract AC activation mediated by a Gs-coupled GPCR.

GRANTEE HONORS AND AWARDS

Kent Berridge, Ph.D., of the University of Michigan, has been elected as Member-at-Large of the Section Committee, Section on Psychology, AAAS. His term began on 20 February 2018.

Michael Bruchas, Ph.D., Henry E. Mallinckrodt Professor, Department of Anesthesiology and Neuroscience, Washington University School of Medicine, received the inaugural Rising Star Award in neuroscience research from the Mahoney Institute for Neurosciences, University of Pennsylvania.

Bertha K. Madras, Ph.D., of Harvard University was awarded the Martin & Toby Adler Distinguished Service Award from the Committee on Problems of Drug Dependence.

Alex Makriyannis, Ph.D., of Northeastern University was awarded the Nathan B. Eddy Award from the Committee on Problems of Drug Dependence.

Margaret McCarthy, Ph.D., of the University of Maryland School of Medicine, has been elected as Member-at-Large of the Section Committee, Section on Neuroscience, AAAS. Her term began on 20 February 2018.

Kathryn McHugh, Ph.D. of the CTN's New England Consortium Node, has been awarded the Theodore Blau Early Career Award for Outstanding Contribution to Professional Clinical Psychology from the American Psychological Foundation. The award honors a clinical psychologist for accomplishments and promise in clinical psychology.

Marina Picciotto, Ph.D., of Yale University, has been elected as Chair-elect, Section on Neuroscience, AAAS. Her term began on 20 February 2018.

Thomas Prisinzano, Ph.D., of the University of Kansas was awarded the Innovator Award from the Committee on Problems of Drug Dependence.

STAFF HONORS AND AWARDS

Dr. Alessandro Bonifazi, Dr. Anver Shaik, and Ms. JoLynn Giancola, all from the Newman lab, received travel fellowships to present their research at the 10th Annual Behavior, Biology, and Chemistry (BBC): Translation Research in Addiction Conference in San Antonio.

Dr. Hank Jedema from the Preclinical Pharmacology section, IRP, received the Kelly Government Solutions Distinguished Achievement Award.

Dr. Chloe Jordan, IRP, received the “Winter Conference on Brain Research Travel Fellow Award” to present her research at the annual Winter Conference on Brain Research in January 2018 in Whistler, Canada.

Dr. Yu (Woody) Lin, of the Integrative Neuroscience Branch of DNB, was selected to receive the 2018 Distinguished Service Award by the Society of NeuroImmune Pharmacology. The award was officially announced at the 2018 joint SNIP/ISNV conference, April 10-14, 2018, Chicago.

Dr. Iván Montoya, DPMC, has been selected to receive the J. Michael Morrison Award from CPDD, June 10th, 2018, San Diego, CA. As a memorial to this well-liked and respected administrator at NIDA, established in 1986, an award is given every other year for outstanding contributions in the area of scientific administration related to drugs of abuse.

Dr. Amy Newman, IRP, was honored at the 255th American Chemical Society National Meeting in New Orleans as a “Remarkable Woman in Medicinal Chemistry.”

Phylicia Porter, DNB, was awarded a Distinguished Achievement Award from Kelly Government Services.

Dr. Rao Rapaka of the Chemistry Pharmacology Branch of DNB was awarded the Inaugural Hall of Fame Award from the Society for Chemistry and Pharmacology of Drug Abuse for contributions and service to the field of Drug Abuse and Medication Discovery.

Dr. Geoffrey Schoenbaum, IRP, gave the Plenary Lecture to open the Winter Conference on Brain Research meeting in January.

Dr. Mel Sharpe won the NIDA-IRP Postdoctoral Excellence in Research Award for her work.

Dr. Yihong Yang, IRP, was elected as a Fellow of the American Institute of Medical and Biological Engineering.

STAFF CHANGES

New Appointments

Kurt Rasmussen, Ph.D., has been selected as the Director of NIDA's Division of Therapeutics and Medical Consequences. Dr. Rasmussen's career spans 28 years of research and leadership experience in pharmacology and neuroscience therapeutics. Dr. Rasmussen received his A.B. in Psychology with honors and distinction from Cornell University and a Ph.D. in Neuroscience and Psychology from Princeton University. He completed his postdoctoral fellowship in the Department of Psychiatry, Yale University School of Medicine. From 1989 to the present, Dr. Rasmussen has been the leader of drug discovery research programs from target identification to Phase III development at Eli Lilly & Co.

Ipolia Ramadan, Ph.D., joined NIDA as a SRO on April 16, 2018. Ipolia received her Ph.D. in Neurobiology at Georgetown University, and after a position as a postdoctoral research fellow at the National Institute on Aging, she joined NINDS as a Health Program Specialist.

Tracy Waldeck, Ph.D. joined NIDA as the Director of the Office of Extramural Policy and Review (OPER), which oversees NIDA's peer review branch, compliance with NIH extramural policies, and coordination of the activities of the National Advisory Council on Drug Abuse. Prior to coming to NIDA, Dr. Waldeck served as the Deputy Director of the Association for Psychological Science, where she was responsible for the effective and efficient functioning of the Association's day-to-day administrative and program operations. In this role, she applied her scientific expertise to the organization's mission, advocated for science funding, and engaged in public outreach aimed at sharing an understanding of psychological science with the public. Before that, Dr. Waldeck served as the Deputy Director of the Division of Extramural Activities (DEA) at the National Institute of Mental Health (NIMH). In her nearly 15-year tenure at NIMH, Dr. Waldeck served in several roles within DEA and was seen the lead policy expert in DEA with particular expertise in extramural program and review policies and matters. Dr. Waldeck graduated from American University and received her Ph.D. in Clinical Psychology from the University of Georgia. She completed a post-doctoral fellowship at Johns Hopkins University, School of Medicine.

Valerie Whipple joined NIDA OM's Station Support Branch as a Supervisory Contract Specialist on April 15, 2018. Valerie comes to NIDA from a position with the National Library of Medicine.

Naresh Chand, D.V.M., Ph.D., moved into the Clinical Research Grants Branch from the Medications Discovery & Toxicology Branch to work on the medical consequences and AIDS/HIV portfolio.

Richard "Rik" Kline, Ph.D. has accepted the position of Branch Chief, Chemistry Pharmaceutics Branch (CPB) in DTMC. Dr. Kline is also the Director of the NIDA Drug Supply program and manages medicinal chemistry, analytical chemistry, dosage form development and production, pharmacokinetics, pharmacodynamics, toxicokinetics and metabolism for the CPB. Prior to joining DTMC in 1998, Rik had over one-year pharmaceutical industry, two years software development industry, and five years academic and government research experience. Rik is a U.S. Marine Corps veteran who received his B.S. in Zoology and Ph.D. in Chemistry from the University of Maryland.

Jinhee Lee, Pharm.D., has been named Deputy Branch Chief of the Public Information and Liaison Branch (PILB) within the Office of Science Policy and Communications (OSPC). Dr. Lee has been leading our science communications team as NIDA's Content Management Director within OSPC. She has greatly improved our outreach to other federal organizations, and has offered innovative and creative contributions by translating many of our new findings into infographics and other consumer friendly products. Jinhee came to NIDA after several years at SAMHSA, where she was the Managing Editor of the Surgeon General's Report on Addiction. She will continue her role coordinating NIDA's public facing content but will take on additional responsibilities as a part of OSPC's leadership team. Jinhee holds a Doctor of Pharmacy degree from University of Illinois, and a Biochemistry degree from UCLA. Jinhee is a Captain in the U.S. Public Health Service Commissioned Corps. Her experience in pharmacology as well as knowledge of the Nation's public health infrastructure will be enormously helpful to the ever-growing demand for the development and dissemination of educational materials related to substance use disorders for multiple audiences.

Departures

Samia Dawud Noursi, Ph.D. is leaving NIDA to become the Associate Director of the NIH Office of Research at Women's Health (ORWH) where she will direct Science Policy and Evaluation in the Office of the Director. She will be responsible for directing, managing and supervising all activities for the following major functions of the Office: science policy, evaluation, relationships and activities related to legislative, advocacy and scientific organizations. At ORWH, Samia will be providing direction for the following ORWH programs in Career Development: the NIH Working Group on Women in Biomedical Careers; the Women's Reproductive Health Research Program (WRHR) and the ORWH/NIH Reentry into Biomedical Research Careers Program. Samia joined NIDA in 2006 and after NIDA's reorganization in 2015, Samia joined DESPR. Since joining DESPR, Samia has been instrumental in managing the portfolio of grants focused on services for women, pregnancy and tobacco at SRB and for the last 8 months serving as the Acting Deputy Branch Chief for SRB. In addition, she has been heavily involved in the SBIR Program and developed concepts that led to several contracts and grants. In addition, she has been co-chairing the NIDA Women and Sex/Gender Differences Research Workgroup and representing DESPR on a variety of committees.

Jermaine Duncan, a Contract Specialist with NIDA OM's Station Support Branch left NIDA on April 28, 2018 for a position with Corporation for National and Community Service.

Ray Hawkins, a Lead Management Analyst in NIDA's Administrative Management and Analysis Branch left NIDA on March 3, 2018 for a position with the Food and Drug Administration.

Nakia Hicks, a Budget Analyst with NIDA's Financial Management Branch left NIDA on February 23, 2018 for a position in the private sector.

Rachelle Trice, a Supervisory Contract Specialist with NIDA OM's Station Support Branch left NIDA on March 17, 2018 for a position with Corporation for National and Community Service.

Retirements

Juanita Nelson, Program Assistant in the Science Policy Branch (SPB), Office of Science Policy and Communications (OSPC), retired after 35 years of Federal service, with almost 18 of those years at NIDA.

Vishnu Purohitt, Ph.D., of the Integrative Neuroscience Branch, DNB, retired March 30 after more than 30 years in government service with 10 years at NIDA.



National Institute
on Drug Abuse